TABLE 1. Changes in Surface Markers of White Cells in Peripheral Blood and Synovia*

Date	10/21	2/27	3/8	4/6	5/2	11/21	12/6	12/13	3/8	5/2	12/9
Mat.	PB	PB	PB	PB	PB	PB	PB	PB	PB	PB	Syn.
Gate	Gr.	Gr.	Gr.	Gr.	Gr.	Mono	Mono	Mono	Mono	Mono	Mono
CD11b	ND	97.5	95.8	98.2	96.6	99.2	94.2	89.6	98.9	98.1	99.6
CD13	ND	89.3	74.0	96.9	90.4	79.9	75.8	81.0	96.4	95.3	81.0
CD14	ND	17.5	>1.0	52.3	3.2	93.0	82.0	ND	13.8	71.5	69.8
CD33	ND	11.2	13.6	97.7	94.9	90.7	72.5	82.2	48.0	99.2	35.8
CD41a	28.1	21.6	10.0	11.7	14.6	77.0	34.0	61.9	43.0	49.0	>1.0

*Mat., material; PB, peripheral blood; Syn., synovia; Gr., granulocyte; Mono, monocyte; ND, not done. Data are shown as positive percentage of gated cells.

Serum Beta-2 Microglobulin as a Marker of B-Cell Activation in Chronic Lymphoid Malignancies

To the Editor: In an attempt to correlate the serum beta-2 microglobulin (β2m) level and the stage of maturation of tumor cells in lymphoid malignancies, we evaluated the β2m levels in 111 patients with chronic lymphoid disorders using a microparticle enzyme immunoassay (Abbott, Abbott Park, IL). Disorders included: prolymphocytic leukemia (PLL) (4 cases), CLL with prolymphocytic features (CLL-PL) 11 cases, typical CLL in various clinical stages (56 cases; 38 in Rai stage 0.1, and 18 in Rai stages 2–4), early myeloma or gammopathy of unknown significance (MGUS) (19 cases), advanced multiple myeloma (21 cases), and 20 normal controls. The level of β2m was significantly higher in patients with PLL (mean 4,421 μg/l, range 3,524–5,580 μg/l) and CLL-PL (mean 3,700 μg/l, range 2,089–6,142 μg/l) compared to controls (mean 1,305, range 803–1,715 μg/l) ($P < 0.01$), early CLL (mean 1,824 μg/l, range 1,040–3,600 μg/l) ($P < 0.01$), advanced stage CLL (mean 2,707 μg/l, range 1,477–4,150 μg/l) ($P < 0.01$), and MGUS and early myeloma (mean 1,714 μg/l, range 1,054–2,805 μg/l) ($P < 0.01$). Highest levels of β2m were observed in the group of advanced myeloma (mean 4,980 μg/l, range 2,600–18,320 μg/l) (Fig. 1).

Beta-2 microglobulin is an 11-kDa protein recognized as the light-chain component of the major histocompatibility complex (MHC) class 1 antigen [1]. It is produced by nucleated cell membranes and is detectable in the serum and other body fluids. The association between the β2m/HLA molecule and membrane structures responsible for lymphocyte activation has been well-defined [2]. The serum β2m level is elevated in a variety of conditions characterized by lymphocyte activation and dysfunction, and

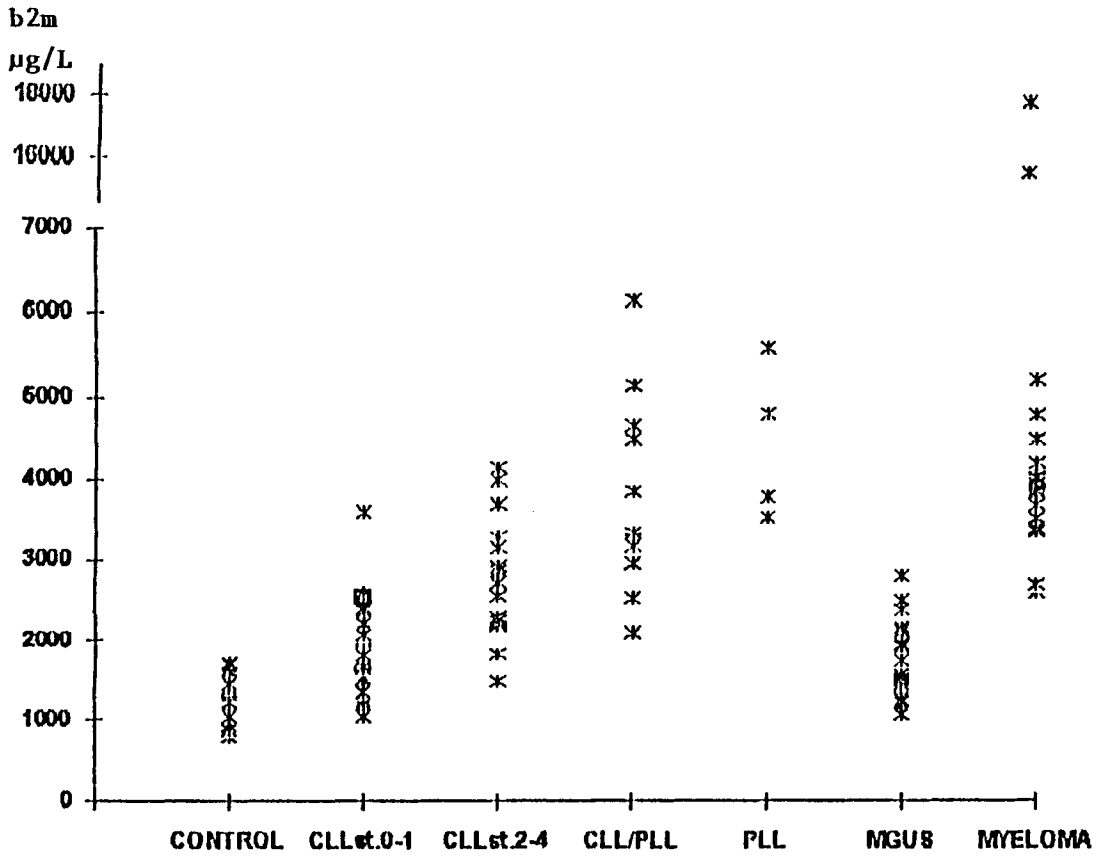

Fig. 1. Values of β2-microglobulin in different groups of patients.

has prognostic value in lymphoid malignancies such as multiple myeloma and CLL. High β2m values in CLL have been found to correlate mainly with stage of disease and high lymphocyte count [3]. Prolymphocytic leukemia is a disease of activated B lymphocytes more differentiated than B-CLL cells. PLL cells express B cell activation antigens CD25, CD38, CD71, FMC7, PCA1, and RAB1 [4]. We found a significantly higher level of β2m in PLL than in CLL patients. Our results indicate that β2m levels may be an additional marker of B-cell activation to further characterize lymphoid diseases arrested in different stages of maturation.

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Fatal Acute Pulmonary Fibrosis in a Patient Treated by Danazol for Thrombocytopenia

To the Editor: Danazol, a synthetic androgen, is used in the management of autoimmune thrombocytopenia not responding to steroids, nor to high-dose intravenous immunoglobulin [1].

We report on the case of a man who had fatal acute pulmonary fibrosis, possibly induced by danazol. This 72-year-old man had a chronic lymphocytic leukemia (CLL), stage A, diagnosed 17 years ago. In September 1994, he developed thrombocytopenia (15×10^9/l platelets). There was neither anemia nor neutropenia. Chest X-ray was normal. He was treated with prednisone (1 mg/kg/day), and platelet count was normal after 10 days. Reduction of dosage of prednisone was associated with lowering of platelet count. So, in order to taper steroid therapy, danazol (100 mg/day) was started in October 1994. In January 1995, when the patient was on prednisone (7.5 mg/day) and danazol, he complained of rapidly worsening breathlessness. Chest X-ray showed bilateral interstitial infiltration. Arterial blood gas analysis showed severe hypoxia. Cytologic analysis of bronchoalveolar fluid revealed normal cellularity without excess of lymphocytes. Histologic examination of surgical lung biopsy showed diffuse pulmonary fibrosis without granuloma, vascularitis, or pathogens. There was no lymphocytic infiltration. Diagnosis was pulmonary fibrosis. Despite high-dose steroid therapy (3 mg/kg/day) and the withdrawal of danazol, the patient's condition deteriorated rapidly, and death occurred 15 days after lung biopsy.

In the absence of an infectious agent and a cause related to CLL, drug-induced pulmonary fibrosis was suspected. Pulmonary symptoms appeared within 3 months of starting danazol therapy. A report suggesting the responsibility of danazol in hypersensitivity lung disease has been published [2]. As in our case, symptoms developed when steroid therapy was withheld, a sequence of events suggesting that prednisone might have protected the lungs from drug aggression.

Although we cannot confirm the responsibility of danazol in this case of acute pulmonary fibrosis, we suggest that patients treated with danazol be advised to report any pulmonary symptom.

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Alpha Genotyping in a Heterogeneous Indian Population

To the Editor: The inherited disorders of hemoglobin (Hb) are the commonest group of single-gene disorders in the Indian subcontinent. Extensive molecular analysis has been undertaken in β-thalassemia among Indians [1]. However, most of the available data on α-thalassemia is based on cord-blood screening for the presence of Hb Bart's. In India, a varied prevalence rate of α-thalassemia ranging from 1–18% has been reported in the general population [2], depending upon the methodology adopted for electrophoresis. A review of the literature reveals a paucity of data on α-genotyping in India. The reports are limited to certain groups of tribal populations having a high prevalence of sickle-cell anemia. Frequency of α-gene deletions in these population groups ranges from 11–81% [3,4].

We determined the α-genotypes in 100 normal individuals and 230 β-thalassemia heterozygotes in a heterogenous caste population (nontribal) from different ethnic groups from various regions in India. DNA was digested with *Bam*HI, and Southern blot hybridization was done using an α Pst probe (1.5 kb) labelled with α^{32}P-dCTP. Cases showing α-gene deletions and triplications were then digested with *Bgl*II to differentiate between the rightward ($-\alpha^{3.7}$) and leftward ($--\alpha^{4.2}$) deletion [5].

The α-globin genotypes found in different regions are shown in Table I. The prevalence of α-thalassemia was 13%, the majority of cases showing a single α-gene deletion of the rightward type ($-\alpha^{3.7}$), except for one case which showed the leftward ($--\alpha^{4.2}$) deletion. α-gene triplication was seen in 2.4% of cases. Regional differences in prevalence of α-thalassemia were seen, although the number of cases in some groups was small, and a larger study is required for a meaningful conclusion. Nevertheless, in the two adjacent regions of Maharashtra and Gujarat, the prevalence of α-thalassemia was significantly different ($P < 0.025$). There was no significant difference in α-genotypes between normal individuals and β-thalassemia heterozygotes ($P > 0.05$). There are only a few reports of HbH disease among Indians, and no case of Hb Bart's hydrops fetalis has been reported so far. This suggests the rarity of a severe α-thalassemia determinant (--) in the general Indian caste population.